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Telephone monitoring of adverse events during an MF59®-adjuvanted H5N1 influenza vaccination campaign in Taiwan

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Keywords: H5N1 influenza vaccine, MF59 adjuvant, vaccine safety, postmarketing surveillance, Taiwan

Abbreviations: TCDC, Taiwan Centers for Disease Control; AEFI, adverse event following immunization; SAE, serious adverse event; OR, odds ratio; CI, confidence interval; ACIP, Advisory Committee on Immunization Practices

This study was conducted to explore a telephone-based approach for identifying and quantifying the occurrence of adverse events following immunization (AEFIs) during an MF59®-adjuvanted H5N1 vaccination program in Taiwan. From March to August 2011, each H5N1 vaccine recipient who voluntarily registered as participants within 72 h of vaccination was phone interviewed at postvaccination 7–10 and 21–24 d. Among the 292 participants, 270 and 263 interviews were completed at 7–10 and 21–24 d. Overall, 127 (48%) respondents reported local and 86 (33%) reported systemic reactions. Females (odds ratio [OR] 2.06, 95% confidence interval [CI] 1.18–3.63), nonelderly adults aged 18–59 y (OR 3.08, 95% CI 1.11–9.45), and first-dose recipients (OR 2.16, 95% CI 1.22–3.86) were independently associated with having an AEFI within the first 7–10 d. None of the AEFIs reported were serious adverse events. In conclusion, most AEFIs to H5N1 vaccine were anticipated but varied with sex, age, and vaccine dose number. The use of modern information technologies will be a scalable alternative to efficiently enroll and monitor recipients with possible AEFIs in large campaigns involving influenza or other emerging vaccines. Further studies should compare the detection of AEFIs using telephone monitoring and standard pharmacovigilance reporting.

Introduction

The establishment of a vaccine stockpile has provided an important opportunity for mitigating the impact of an H5N1 pandemic.[1] In Taiwan, the stockpiled vaccine is an MF59®-adjuvanted, inactivated, subunit H5N1 product derived from the A/Vietnam/1194/2004 (H5N1)-like strain (Novartis Vaccines and Diagnostics).[2] This vaccine has been licensed in Europe for pandemic vaccination of adults and is procured by Taiwan Centers for Disease Control (TCDC) under a special-use authorization.

The monitoring of spontaneous adverse event following immunization (AEFI) reports for human vaccines in routine use has been collaboratively conducted by TCDC and Taiwan Food and Drug Administration.[3] In 2011, TCDC developed a voluntary H5N1 vaccination program to immunize agencies and occupational groups who perform essential social functions and who are at risk of being exposed to H5N1 virus. This program provides an opportunity to improve our very limited understanding of the H5N1 vaccine safety. We also explore a telephone-based approach to identify and quantify the occurrence of AEFIs in support of existing postmarketing surveillance systems in Taiwan.[3]

Results

As of August 2011, 22 403 doses of MF59®-adjuvanted H5N1 vaccine were administered. The existing spontaneous reporting system received eight reports of adverse events after H5N1 vaccination; none were categorized as SAEs. Reported adverse events were local reaction, dizziness, and influenza-like illness.

A total of 292 H5N1 vaccine recipients registered as participants (**Table 1**); 270 and 263 interviews had been completed at 7–10 and 21–24 d of vaccine administration. Overall, 127 (48%) respondents reported local reactions and 86 (33%) reported systemic reactions; none of the AEFIs were SAEs. The median days between H5N1 vaccination and onset of an adverse event was 0 (range 0–20). At 7–10 d, the most frequently reported solicited local and systemic reactions were pain (109, 40%) and fatigue (40, 15%), respectively (**Fig. 1**). Unsolicited AEFIs that occurred in ≥3 respondents included cough (20, 8%), upper respiratory tract infection (12, 5%), dizziness (11, 4%),

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Table 1. Characteristics of 292 study participants

Characteristic	Number of participants	(%)
Sex		
Male	108	(37)
Female	184	(63)
Age		
18–59 y	266	(91)
≥60 y	26	(9)
Dose		
First	202	(69)
Second	90	(31)
Received 2010–11 seasonal influenza vaccination		
Yes	235	(80)
No	56	(19)
Unknown	1	(< 1)
ACIP high-risk conditions[a]		
Yes	42[b]	(14)
No	250	(86)

ACIP, Advisory Committee on Immunization Practices. [a]Conditions associated with increased risk for serious medical complications from influenza.[4] [b]Including cardiovascular (n = 10), chronic asthma or other pulmonary (n = 12), diabetes mellitus or other metabolic (n = 9), neuromuscular (n = 4), and hepatic (n = 10) disorders.

oropharyngeal pain (11, 4%), rhinorrhea (11, 4%), diarrhea (10, 4%), and dry throat (3, 1%).

Of the 270 participants who completed the postvaccination days 7–10 interview, females (odds ratio [OR] 2.06, 95% confidence interval [CI] 1.18–3.63), nonelderly adults aged 18–59 y (OR 3.08, 95% CI 1.11–9.45), and subjects receiving their first dose of H5N1 vaccine (OR 2.16, 95% CI 1.22–3.86) were independently associated with having an AEFI within the first 7–10 d of vaccination (**Table 2**).

Discussion

Although prepandemic vaccination of higher risk groups has been recommended by the World Health Organization,[1] concerns over adverse events remain a major barrier to H5N1 vaccination in advance of a pandemic.[5-7] This study contributed to the limited understanding of adverse events following MF59®-adjuvanted H5N1 vaccination, particularly outside the clinical settings. Its findings were consistent with prelicensure observations;[2,8] the reported AEFIs were common, nonserious, and anticipated. Also, AEFI occurrences varied with sex, age, and vaccine dose number.

Passive surveillance frequently involves underreporting, biased and incomplete data. Active AEFI monitoring supplements the spontaneous reporting system and in Taiwan, has been implemented by linking vaccination and healthcare databases to evaluate the safety of 2009 H1N1 monovalent vaccines.[3,9] In mass vaccination campaigns, individual immunization records usually are not captured by the computerized registries, particularly when the vaccines are administered outside the traditional provider offices.[3] Thus, one of the challenges is that ad hoc registration of vaccination data for linkage studies can entail delays in identifying potential vaccine safety concerns. Direct patient follow up, through telephone or computer-assisted interviews, has been used to actively monitor postlicensure safety for vaccine recipients.[10-12] In this telephone monitoring study, recipients of H5N1 vaccine

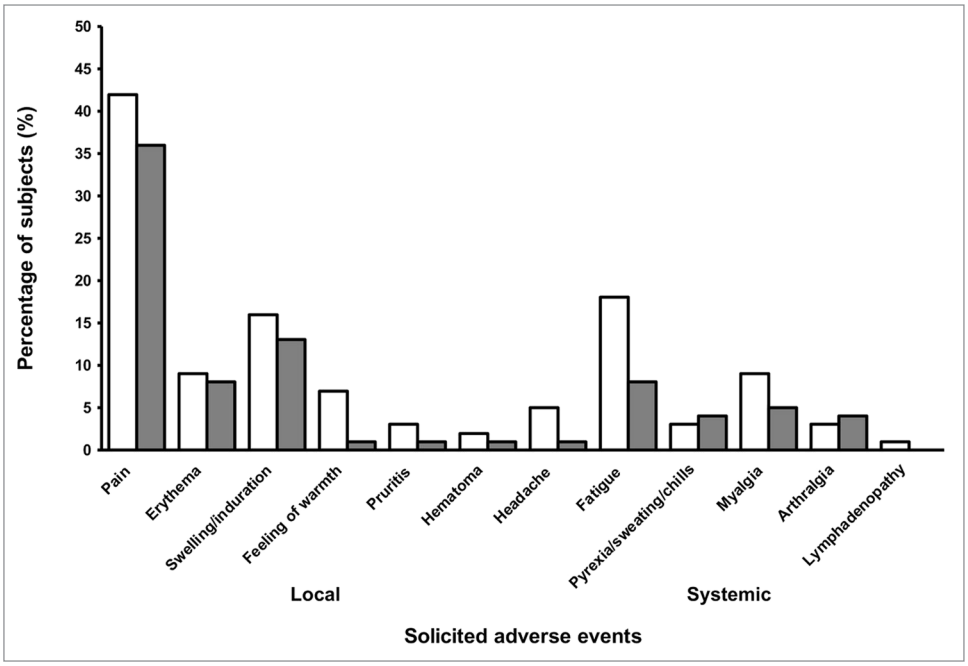

Figure 1. Solicited local and systemic reactions reported within 7 to 10 d after A/H5N1 vaccination. Classified by symptom after the first (white bars) or second (gray bars) vaccination in study participants.

Table 2. Factors associated with the occurrence of adverse events within 7 to 10 d of A/H5N1 vaccination

Variable	Number of participants	Number of patients with adverse events	Univariate OR (95% CI)	Multivariate OR[a] (95% CI)
Sex				
Male	98	46	Reference	Reference
Female	172	117	2.40 (1.40–4.13)	2.06 (1.18–3.63)
Age				
18–59 y	247	156	3.90 (1.45–11.64)	3.08 (1.11–9.45)
≥60 y	23	7	Reference	Reference
Dose				
First	186	124	2.30 (1.32–4.04)	2.16 (1.22–3.86)
Second	84	39	Reference	Reference
Received 2010–11 seasonal influenza vaccination				
Yes	213	131	1.12 (0.59–2.09)	-
No	56	32	Reference	-
ACIP high-risk conditions				
Yes	39	22	Reference	-
No	231	141	1.21 (0.57–2.53)	-

OR, odds ratio; CI, confidence interval; ACIP, Advisory Committee on Immunization Practices. [a]Adjusted for variables listed.

were recruited early after vaccination and followed throughout the 21–24 d postvaccination to collect their demographics and AEFI occurrences in near real-time. Although the small number of participants did not report any new syndromes or SAEs, this approach could be complementary to that of data linkage by providing timely information to assist early detection of adverse events that might be associated with vaccination.

Making follow-up contacts and manual data entries by study staff, however, was labor intensive. Automated telemedicine systems have offered interactive voice response, internet, or mobile text message alternatives and will be more feasible to efficiently enroll vaccinees and monitor patient-reported symptoms over a short period of time.[11,12] If a particular vaccine safety concern arises, the readily available data sets on the vaccinated case-patients can be used to rapidly evaluate whether vaccination is associated with an increased risk of that outcome by two case-only designs, the case-centered and the self-controlled case series methods.[13,14]

A telephone-based approach to collect safety data may not be practical in developing countries or in areas whether telephone usages are limited. Also, this approach may not be very useful for collecting detailed safety data of the adverse reactions as in a diary card. This study has other limitations. First, the authors did not assess the severity of reported AEFIs; for example, the diameter of the local reaction. The occurrence of pyrexia/sweating/chills was self-reported instead of asking for a measured temperature. Second, it was based on a relatively small number of vaccines that would not allow detection of rare and serious events. For rare adverse events that occurred with a background rate of 1:100, a sample size of 6618 and 1030 study participants would be necessary to have 80% power to allow the identification of a least detectable relative risk of 2.0 and 5.0, respectively, using the self-controlled case series method.[15] Third, recipients of H5N1 vaccine were enrolled based on their willingness to participate. The low participation rate might have introduced selection bias, over representing persons with AEFIs and would have overestimated the adverse event rates. Finally, actively asking for specific events could be suggestive and was subject to recall bias; the outcomes were self-reported and unvalidated.

In conclusion, active telephone monitoring of AEFIs offers the advantage of rapid identification and timely follow-up of these events; it can be complementary to existing postmarketing surveillance systems in Taiwan. No new or unexpected adverse events were observed following receipt of MF59®-adjuvanted H5N1 vaccine in this study although our cohort size was not large enough to assess for any rare AEFIs. The government should consider using modern information technologies as a scalable approach to efficiently enroll and monitor recipients with possible AEFIs in large campaigns involving influenza or other emerging vaccines. Further studies should compare the detection of AEFIs using telephone monitoring and standard pharmacovigilance reporting.

Materials and Methods

Targets of MF59®-adjuvanted H5N1 vaccination included healthcare workers, poultry workers, quarantine and immigration officials, and travelers to countries in which outbreaks of highly pathogenic H5N1 avian influenza had been reported. Beginning March 1, 2011, the H5N1 vaccine was distributed to the designated immunization clinics at which eligible adults ≥18 y of age could voluntarily choose to receive two vaccine doses, administered ≥3 weeks apart.

Recipients of H5N1 vaccine were recruited through August 31, 2011. At the time of vaccination, an information sheet was

provided to H5N1 vaccine recipients and requested interested vaccinees to call TCDC within 72 h of vaccination using the toll-free hotline "1922." Consent to participate in the study was obtained during the initial telephone interview. If respondents were willing to be contacted for possible AEFIs, the interview would proceed with asking questions about their age, sex, date, and dose number of the received H5N1 vaccination, receipt of 2010–11 seasonal influenza vaccine, underlying medical conditions,[4] and a telephone number at which they could be reached by study staff on subsequent follow-up.

The telephone interviews were conducted through September 30, 2011. Attempts were made to contact participants during the postvaccination days 7–10 and 21–24 interview periods. At each interview, we actively asked for solicited local reactions (pain, erythema, swelling or induration, feeling of warmth, pruritus, and hematoma) and systemic reactions (headache, fatigue, pyrexia/sweating/chills, myalgia, arthralgia, and lymphadenopathy) that occurred through the time of their vaccination or from the last interview; other unsolicited AEFIs were filled in as free text. If participants reported a serious adverse event (SAE) involving death, life-threatening illness, hospitalization, prolongation of hospitalization, permanent disability, or congenital anomaly,[16] the event would be verified and handled according to the TCDC guidance for SAEs.

The data were analyzed using SAS®, version 9.2 (SAS Institute Inc.). We calculated participant characteristics, solicited local and systemic reactions, and time to onset and outcome of the adverse events. Tests for association between potential risk factors and developing AEFIs within 7–10 d of H5N1 vaccination were performed using multivariate logistic regression, and backward elimination procedures retained variables that were associated at $P < 0.10$ to develop the model.

According to Articles 26 and 28 of the Communicable Disease Control Act in Taiwan,[17] data collection for this study was conducted as part of a public health response to the H5N1 vaccination program and did not require approval by an institutional review board.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Contributors

All authors participated in the concept and design, analysis, and interpretation of data, drafting or revising the manuscript, and they have approved the manuscript for publication

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